CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
ACTIVE INGREDIENT(2,4-DB)
4-(2,4-Dichlorophenoxy)butyric acid (IUPAC) †

Chemical Code # 838, Tolerance # 50720
SB 950 # 622 (SEE BELOW FOR ADDITIONAL CHEMICAL IDENTIFIERS FOR 2,4-DB)

7/19/99

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effects
Chronic toxicity, dog:	No data gap, no adverse effects
Oncogenicity, rat:	No data gap, no adverse effects
Oncogenicity, mouse:	No data gap, no adverse effects
Reproduction, rat:	No data gap, possible adverse effects
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, possible adverse effects
DNA damage:	No data gap, possible adverse effects
Neurotoxicity:	Not required at this time

† Chemical names and structure are described in Farm Chemicals Handbook '99. The test article is variously identified in studies below as 2,4-DB or 4-(2,4-DB). This Summary typically uses the designation utilized in the cited report.

Toxicology one-liners are attached.

Data relating to this Summary for (2,4-DB) represent studies supporting only two salts/esters, only one of which is actively registered (the dimethylamine salt: Tolerance No. 838). The other active registration is the free acid (Tolerance No. 5020). No chronic data have been submitted under the latter Tolerance Number. The DPR library lists two additional chemical codes for (2,4-DB). Some data had been submitted under one of these (Chemical Code 837: Tolerance No. 331). Since the latter a.i. is no longer registered, all data available for 2,4-DB are now

maintained under Tolerance No. 838. The following table was made from information in the DPR Registration Branch Data Base as of 1/26/99.

Chemical Code	Tolerance No.	DPR Activity Status	Relevant FIFRA Data?
838	50720	Active	Yes
837	331	Inactive	Yes
5020	N/A	Active	No
1385	N/A	Inactive	No

All record numbers for the above study types through 113572 (Document No. 50720-037) were examined. This includes all relevant studies indexed by DPR as of 7/13/99.

In the 1-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: t990719.wpd
Produced by C. Aldous, 7/19/99

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED (CHRONIC AND ONCOGENICITY), RAT

50720-037 113572 MacKenzie, K. M., "Lifetime dietary combined chronic toxicity and oncogenicity study in albino rats with 2,4-DB", Hazleton Laboratories America, Inc., Madison, WI, 5/28/87. Laboratory Study # HLA 6158-103. Crl:CD®(SD)BR rats, 50/sex/group, were dosed in diet with 0, 60, 600, or 1800 ppm for 2 years for the oncogenicity study. In addition, there were 20/sex/group for chronic toxicity study (used for hematology, clinical chemistry, and urinalysis at 3, 6, 12, 18, and 24 months), 10/sex/group for a 1-yr interim sacrifice, and an additional 10/sex/group were taken off treatment after 1 yr of treatment for 4 weeks of recovery prior to sacrifice at 13 months. NOEL = 60 ppm [modest food consumption and body weight reductions (F), and reductions in circulating cholesterol (M & F) and globulins (F)]. High dose levels exceeded the MTD. This was prominently reflected in female total body weights, which were reduced by 21% at 1 year, compared to an 8% reduction in males at that time. High dose rats had reductions in circulating glucose, proteins (especially globulins), and cholesterol, as well as reductions in RBC parameters (F) and in platelet counts (M & F). The only remarkable increase in histopathology was incidence of infarcts in kidneys of high dose males. None of the above changes appear to relate to specific target organ responses. The great majority of high dose histopathology changes were **reductions of normal aging-related changes in females. The study is acceptable, with no adverse effects. Kishiyama and Aldous, 7/2/99.

331-007 59223 Exact duplicate of 50720-037 113572, above.

CHRONIC TOXICITY, DOG

50720-020 095291 Hamada, N. N., "One-year oral toxicity study in beagle dogs with 2,4-DB Technical", Hazleton Laboratories America, Inc., 9/12/90. HLA Study No. 400-724. Six purebred beagles/sex/group were dosed in diet with 0, 75, 225, or 450 ppm 2,4-DB for 1 year (the high dose group began the study at 675 ppm, which proved excessive based on marked body weight and food consumption decrements, therefore this dose was reduced to 450 ppm from week 7 until termination of dosing). The adjustment to 450 ppm proved to be sustainable. Standard chronic observations were undertaken during the study. Four/sex/group were sacrificed at 1 year, whereas the other 2/sex/group were retained for 4 weeks off treatment for a recovery study in response to the pattern of clinical chemistry responses (below). No NOEL was identified for events occurring during the dosing period. Findings at 75 ppm included elevated serum levels of BUN, creatinine, and ALT; also an increase in degree of pigmentation of renal tubule cells. Additional common histopathology findings at 225 ppm and above included pigmentation of Kupffer cells and hepatocytes. Findings mainly restricted to the high dose dogs included reductions in hematology readings (particularly red cell parameters), and an increase over the background level of chronic inflammation of the liver. None of these findings were evident after the 4-week recovery period, except slightly elevated ALT and slight elevations over background levels of pigmentation in livers and kidneys of 450 ppm females. Study is **acceptable, with **no adverse effects**. Aldous, 7/13/99.

ONCOGENICITY, MOUSE

**50720-036 113570 MacKenzie, K. M., "Lifetime dietary combined oncogenicity study in albino mice with 2,4-DB", Hazleton Laboratories America, Inc., Madison, WI, 5/18/87. Laboratory Study # HLA 6158-104. Crl:CD-1®(ICR)BR mice, 50/sex/group, were used for 18-month oncogenicity evaluation at 0, 25, 250, and 750 ppm. An additional 20/sex/group were allocated for a 1-yr interim sacrifice. NOEL = 25 ppm. Statistically significant increases in amyloidosis in males, particularly in liver and heart, were found in non-survivors at 250 and 750 ppm. Significant increases above normal incidences of amyloidosis were also observed in 750 ppm males in many tissues at 12-month sacrifice. A reduced survival among 750 ppm males indicates that the MTD had been exceeded at that dose level: perhaps in part through increased incidence of renal amyloidosis. Other changes at that dose included altered differential blood counts (elevated percentage of segmented neutrophils and lower percentage lymphocytes) in high dose males, and elevated kidney weights in both sexes. No adverse effects are indicated. There was no oncogenic effect. Acceptable. Aldous, 7/6/99.

331-006 059222 Exact duplicate of Record No. 113570, above.

REPRODUCTION, RAT

****50720-035 113569** Bottomley, A. M., A. J. Bowman, J. M. Offer, W. A. Gibson, A. Anderson, I. S. Dawe, "2,4-DB - Effect on two generations of the rat", Huntingdon Research

Centre, Ltd., 6/26/86, Laboratory Project ID # UNC/138-R. Crl:COBS CD®(SD) BR rats, 28/sex/group, were dosed at 0, 60, 300, or 1500 ppm for 2 mating trials of the F0 parents. The 1500 ppm group did not produce sufficient F1 animals to continue that dose level. F1b parental rats, 24/sex/group, were used in 2 mating trials at remaining dose levels. The most sensitive response in parental rats was a minor degree of dorsal hair loss or thinning in 2 females at 300 ppm: a finding of insufficient importance for setting the systemic NOEL. Along with this characteristic finding, 1500 ppm yielded reduced food consumption and reduced body weights in both sexes, and increased water consumption in females. F0 1500 ppm rats had increased kidney weights, and females had decreased adrenal and ovarian weights. Pup NOEL = 300 ppm (pup growth was severely reduced and pup deaths occurred throughout the lactation period); **"possible adverse effects"**. Study is **acceptable**, with deficiencies as indicated in the review. The primary weakness of this study was the wide spread between dose levels, so that the data provide limited dose-response information. There were no definitive findings in adults nor were there changes in reproductive parameters at the NOEL of 300 ppm. Aldous, 7/8/99.

331-008 059224 Duplicate of 50720-035 113569, above.

TERATOLOGY, RAT

50720-028 092057 Rodwell, D. E., "Teratology study in rats with Butyrac 200", Springborn Laboratories, Inc. (SLS), Spencerville, OH., Report # 3147.54, Jan. 3, 1991. Groups of 25 presumed pregnant Crl:CD® BR VAF/Plus® rats were dosed with 0, 31.25, 62.5, or 125 mg/kg/day of Butyrac 200 [25.8% 4-(2,4-DB) by weight: doses were adjusted to 100% a.i.] by gavage on gestation days 6 through 15. Cesarean sections were done on day 20 in a standard teratology study protocol. Maternal NOEL = 31.25 mg/kg/day (modest body weight and food consumption reductions, and associated clinical observations of "few feces"). Developmental NOEL = 62.5 mg/kg/day (reduced live litter size and reduced fetal weights). High dose maternal toxicity was characterized by decreased activity, hunched posture, and 2 cases of ataxia. Food consumption and body weights were sharply reduced, and 6 dams showed "no feces" during the treatment period. Three of these high dose dams died or were sacrificed prematurely due to treatment. Cesarean section data showed reductions in mean litter size and mean fetal weight, as well as two total litter losses at 125 mg/kg/day. Skeletal malformations (rib and vertebral anomalies) were limited to high dose fetuses (7 fetuses and 3 litters were affected at 125 mg/kg/day, vs. none in other groups). Variation increases such as 14th full ribs and 7th cervical ribs were also elevated in high dose litters. These developmental changes were attributed to treatment, and considered by investigators to result from maternal toxicity. There were no treatment-related developmental findings except at highly toxic levels. There is no indication of developmental toxicity which is not plausibly associated with maternal toxicity, hence **no adverse effects. **Acceptable**. (H. Green and C. Aldous, 7/2/99).

50720-027 092056 Rodwell, D. E., "Range-finding teratology study in rats with Butyrac 200". Pilot study for Record No. 092057, above [Springborn Laboratories, Inc. (SLS), Report # 3147.53, Jan. 3, 1991]. Most dams died at the high dose of 275 mg/kg/day, and many dams at the next highest dose of 175 mg/kg/day had clinical signs of ataxia, decreased activity, and/or reddish vaginal discharge. The latter dams' body weights were reduced 12% to 19% during treatment. Total litter resorption incidence was increased and fetal weights were

reduced at 175 mg/kg/day. Dose levels chosen for the primary study were rationally selected, based on these results. More details on this pilot study are in the worksheet for Record No. 092057, as summarized by H. Green.

****50720-012 090378** Henwood, S. M., "Teratology study with 2,4-DB acid in rats", Hazleton Laboratories America, Inc.,1/30/90, Laboratory Study # HLA 6224-143. Twenty-five Crl:CD®BR dams/group were dosed by gavage with 0, 31.25, 62.5, or 125 mg/kg/day of 4-(2,4-DB) acid (98.1%) on gestation days 6-15. Maternal NOEL = 62.5 mg/kg/day (one maternal death; clinical observations including emaciation, languid, hunched, poor muscle tone, and piloerection; and substantial body weight decrement). Developmental NOEL = 31.25 mg/kg/day (ossification delays at 62.5 mg/kg/day). Four 125 mg/kg/day dams had total resorptions, and resorption incidence in remaining litters was somewhat higher than controls. There were increased soft tissue malformations at 125 mg/kg/day, with microphthalmia and anomalies involving the aortic arch being most common. No single soft tissue malformation was increased significantly in frequency, however investigators justifiably considered these collective changes to be treatment-related. Some skeletal malformation incidences were elevated at 125 mg/kg/day. These included fused cervical arches or thoracic arches, and malformed or misshapen ribs. The study indicates a "possible adverse effect", based on a lower NOEL for developmental toxicity than for maternal toxicity. Since only developmental ossification delays were significantly elevated at the developmental LOEL (62.5 mg/kg/day), this result should not evoke unusual concern. Developmental toxicity at 125 mg/kg/day was very plausibly due to high maternal toxicity. Acceptable. Aldous, 7/2/99.

50720-012 090377 Pilot study for 50720-012 090378, above. In this pilot study, 5/5 died or were sacrificed *in extremis* at dose levels of 500 and 1000 mg/kg/day, and 4/5 dams did not survive at 250 mg/kg/day. All dams survived at 125 mg/kg/day, and this group had reduced maternal body weight gain during pregnancy. This group had elevated early resorptions compared to other groups. The dose levels chosen for the primary study were justified, based on this pilot study. Aldous, 1/27/99 (this study is cited in the worksheet for Record No. 090378).

SUMMARY: Two acceptable rat teratology studies have been submitted. The study employing 2,4-DB acid was classified as indicating a "possible adverse effect", based on a lower NOEL for developmental toxicity than for maternal toxicity. It was noted in that review (Record No. 090378) that the developmental NOEL was based on ossification delays. The high dose of 125 mg/kg/day in that study caused overt maternal toxicity, and one maternal death. Four litters with total litter losses, increased pre-natal losses in litters with viable pups, and increased soft tissue malformations occurred at 125 mg/kg/day in that study. The study using Butyrac 200 (the dimethylamine salt of 2,4-DB: Record No. 092057) likewise showed severe maternal toxicity at125 mg/kg/day (adjusted to 100% a.i.). The latter study did not reveal malformations at even the highest dose level, and found no developmental toxicity at 62.5 mg/kg/day, despite maternal toxicity at that dose level. Collectively, the two studies do not warrant a "possible adverse effect" designation for rat developmental studies. Aldous, 7/13/99.

TERATOLOGY, RABBIT

**50720-015 091009 Henwood, S. M., “Teratology study with (2,4-DB) acid in rabbits”, Hazleton Laboratories America, Inc. (Madison, WI), 5/29/90, Study ID: HLA 6224-145. Sixteen artificially inseminated Hra:(NZW)SPF does per group were dosed at 0, 15, 30, or 60 mg/kg/day (2,4-DB) acid (98.1%) by gavage on gestation days 7-19. Maternal NOEL = 30 mg/kg/day (two abortions and two deaths *in extremis*, associated clinical signs including body weight decrements, loss of coordination, ataxia, inactivity, and reduced or absent fecal output). Developmental NOEL = 60 mg/kg/day (no observed effects). Study is acceptable. No adverse effects. Aldous, 7/7/99.

50720-014 091008 Henwood, S. M., (range-finding study for Record No. 091009), 02/28/90, Study ID: HLA 6224-144. There were no survivors at 200 to 400 mg/kg/day, 2/8 survived at 100 mg/kg/day, and 7/8 survived at 50 mg/kg/day. Many of the clinical observations at 50 to 100 mg/kg/day were similar to those of the primary study. Body weights of 50 mg/kg/day does were significantly reduced. Several 100 mg/kg/day does had stomach erosions when necropsied. Uteri were examined for resorptions and fetal viability status, and live fetuses were examined externally only. There were no definitive developmental effects. Dose levels chosen for the primary study are justifiable. Aldous, 1/29/99 (no DPR worksheet).

331-004 037335 Weatherholtz, W. M., “Segment II - Teratology - Rabbits: 2,4-DB Acid”, Hazleton Laboratories, Inc., 11/6/70, Project # 656-117. Eleven or twelve NZW rabbits/group were dosed by gelatin capsule on days 6 through 18 of gestation with 0, 12, or 60 mg/kg/day 4-(2,4-DB) acid. About half of the does were sacrificed on day 30 for teratology evaluation, and the rest were allowed to litter. Two high dose dams died (plausibly due to treatment). Three to 8 dams per group were not pregnant. Only 1 high dose doe was pregnant and terminated by cesarean section. Study is **not acceptable**, and **not upgradeable**. Mortality at 60 mg/kg/day has been confirmed in a later study (Record No. 091009). There was otherwise no important, interpretable information obtained in this study. Aldous, 7/13/99.

TERATOLOGY, MOUSE

331-004 037336 Weatherholtz, W. M., “Segment II - Teratology - Mice: 2,4-DB Acid”, Hazleton Laboratories, Inc., 10/28/70. Project # 656-118. Twenty female “Charles River Mice” per group were assigned to dose levels of 0, 400, or 2000 ppm 4-(2,4-DB) acid in diet during gestation days 6-15. Mice were sacrificed on day 17 of presumed gestation. About one third of fetuses per litter were examined for soft tissue changes, the rest were used for skeletal examinations. One high dose female died, and another which survived was cold to touch near to the end of the treatment period. Two high dose dams had total litter losses: one had only resorptions and another had only dead fetuses. There was no tabular presentation of developmental responses, and the text did not identify treatment effects. Mean weights and lengths of fetuses were smaller in the high dose group compared to other groups. Aside from identifying maternal and associated developmental toxicity at 2000 ppm, this study does not provide useful data. **Unacceptable and not upgradeable, with “no adverse effects” indicated**. Aldous, 7/13/99.

GENE MUTATION

50720-010 085099 Lawlor, T. E., and L. Haworth, "Mutagenicity test on Butyrac 200 in the Ames Salmonella/microsome reverse mutation assay", Hazleton Laboratories America, Inc., 9/13/89, HLA Study # 10814-0-401. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 were exposed to 0, 250, 500, 1000, 2500, 5000, or 10000 µg/plate Butyrac 200 (25.8% 2,4-DB by weight) in an Ames test with and without S9. The highest treatment level typically proved cytosolic under test conditions. No mutagenicity was indicated based on lack of revertant production in the test range. Positive controls were functional. Useful supplementary data, not applicable to FIFRA data requirements, since test article was not the technical active ingredient. Kishiyama and Aldous, 7/6/99.

**331-009 059226 Jagannath, D. R., "Mutagenicity test on 2,4-DB Technical 98.03% Lot #RTC 5838AA in the Ames Salmonella/microsome reverse mutation Assay", Hazleton Laboratories America, Inc., 5/20/87. HLA Study No. 9360-0-401TR. 2,4-DB technical, 98.03% purity, was tested at concentrations of 0 (DMSO), 1, 10, 100, 500, 1000, 2500, 5000, or 10000 µg/plate in the presence and absence of metabolic activation (S9 Mix) in the Ames test with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538. Exposure time was 48-72 hours. Two independent trials contained 3 reps per concentration. 2,4-DB technical trials did not increase the number of histidine revertants/plate in any strain in either trial. Acceptable, with no adverse effects. Kishiyama and Aldous, 7/8/99.

**50720-024 091864 Young, R. R., "Mutagenicity test on Butyrac 200 in the CHO/HGPRT forward mutation assay", Hazleton Laboratories America, Inc., HLA Study # 10814-0-435, 7/20/90. Chinese hamster ovary cells (CHO-K1-BH4 subclone) were exposed for four hours in the presence or absence of S9 activation at concentrations ranging from 0.05 to 5.0 mg/ml Butyrac 200 (26% 2,4-DB salt: the particular concentrations varied slightly from trial to trial). There was no pattern suggestive of a treatment effect on mutant frequency. Acceptable, with deficiencies as noted. No adverse effects. (H. Green and C. Aldous, 7/8/99).

331-009 059225 Young, R. R., "Mutagenicity test on 2,4-DB, Technical Lot Number RTC 5838AA in the CHO/HGPRT forward mutation assay", Hazleton Laboratories America, Inc., 6/10/87. HLA Study # 9360-0-435. 4-(2,4-DB) technical, Lot No. Lot #RTC 5838AA (described in other studies to represent 98.03% purity) was tested primarily in the range of 0.5 to 1.0 mg/ml, which levels bracketed the cytotoxic range. Two trials conducted without S9 activation were negative. Three trials were conducted with S9. There were more statistically significant increases than would be expected by chance, however the data lacked consistent response patterns. The study author concluded that the assay was negative, based on the low concurrent vehicle control values in the third trial with S9 compared to historical controls, and lack of reproducibility between duplicate cultures. The latter observations are correct, and the study is classified as unacceptable, with data quality too poor to make a meaningful assessment for possible adverse effects (see worksheet Discussion Section). Aldous, 7/8/99.

CHROMOSOME EFFECTS

****331-009 059227** Ivett, J. L., "Mutagenicity test on 2,4-DB Tech 98.03% in an *in vitro* cytogenetic assay measuring chromosomal aberration frequencies in Chinese hamster ovary (CHO) cells", Hazleton Laboratories America, Inc., 5/20/87. HLA Study # 9360-0-437. Chinese hamster ovary (CHO-WBL) cells were treated with 250, 500, 750 or 1000 µg/ml 2,4-

DB Tech with and without rat liver S9. Dose levels and incubation times had been determined by a preliminary test. No indication of chromosomal aberration was evident with S9, however a sharp and definitive increase in % cells with aberrations was found at 750 or 1000 µg/ml 2,4-DB Tech without S9 activation. Acceptable, with a "possible adverse effect". Aldous,7/8/99.

331-005 052081 [an earlier version Record No. 059227, above, which is the final (amended) version].

50720-010 085100 Murli, H., "Mutagenicity test on Butyrac 200 in an *in vitro* cytogenetic assay measuring chromosomal aberration frequencies in Chinese hamster ovary (CHO) cells", 7/28/89. HLA Study # 10814-0-437. Chinese hamster ovary (CHO-WBL) cells were treated with 1000, 2000, 3000, or 4000 µg/ml Butyrac 200 (25.8% a.i.) with and without rat liver S9. Dose levels and incubation times had been determined by a preliminary test. No indication of chromosomal aberration was evident with S9, however a significant increase in % cells with aberrations was found at 4000 µg/ml Butyrac 200 in the absence of S9. This was considered not to be treatment-related by investigators, considering the closeness of the result to the range of control data. Since a previous Hazleton study had found 4-(2,4-DB) Technical (98.03%) to have elicited chromosomal aberrations in the absence of S9 (HLA Study No. 9360-0-437, DPR Document/Record Nos. 331-009/059227), the present positive finding cannot be discounted by DPR. In both studies, positive effects were limited to dose levels which slowed down cell cycle and which reduced cell confluence. Useful supplementary data, not applicable to FIFRA data requirements, since test article was not the a.i. The study indicates a "possible adverse effect". Aldous, 7/6/99.

DNA DAMAGE

****50720-033 087965** [formerly mistakenly classified as a 2,4-D chemical under DPN No. 50723-004] "Mutagenicity Test on Butyrac 200 in the Rat Primary Hepatocytes Unscheduled DNA Synthesis Assay" (M. A. Cifone, Hazleton Laboratories America, MD, Study No. 10814-0-447, 9/26/89) Butyrac 200, Lot #50215906, no purity given, was assayed with male Fischer 344 rat hepatocytes at 15 concentrations ranging from 5030 to 0.503 µg/µl. Six concentrations at and below 252 µg/µl were analyzed. Triplicate cultures were scored, 50 cells/culture. At 252 µg/µl, survival was 79% and an average of 23.3% of the nuclei had more than 6 grains. **Possible adverse effect**, an increase in UDS. Originally reviewed as unacceptable but upgradeable with submission of individual data and compound purity. These data were provided in Record No. 113508, below. Study is now **acceptable** (Gee, 7/25/91, 2/8/99).

50720-034 113508 Addendum to Document # 50720-033, Record # 087965. "Mutagenicity Test on Butyrac 200 in the Rat Primary Hepatocytes Unscheduled DNA Synthesis Assay [Additional Data]" [HWA Study # 10814-0-447]. Supplemental report date: 3/11/92. The original Medical Toxicology Branch review of 7/25/91 had requested test article characterization and individual data. This response provided a certificate of analysis, showing test article to be "26.7% (wt/wt) 2,4-DB DMA salt". In addition, response provided summary data of percent cells with $ 5 mean net nuclear grain count for the original study, plus solvent control and positive control data. Individual grain count data were also provided. These data allow an upgrade of the cited study. There is no change in the study interpretation (an increase in UDS at the higher two treatment levels). Gee and Aldous, 2/8/99.

**331-009 059228 Cifone, M. A., “Mutagenicity test on 2,4-DB Technical, 98.03% in the rat primary hepatocyte unscheduled DNA synthesis assay”, Hazleton Laboratories America, Inc., 5/20/87. HLA Study No. 9360-0-447. 2,4-DB technical was assayed for UDS with rat hepatocytes at concentrations of 2.49, 4.99, 9.97, 24.9, 49.9, or 99.7 µg/ml. Exposure time for hepatocytes to 2,4-DB treatments was 18-19 hours. No UDS response with 2,4-DB treatments. Cell survival was 62.5% or greater for 2,4-DB treatments. Acceptable, with deficiencies as noted. No adverse effects. Kishiyama and Aldous, 7/8/99.

NEUROTOXICITY

Not required at this time.

STUDIES EXAMINED BY PRODUCT DATA REVIEW GROUP
(not study types required under SB-950)

50720-018;-022; 88873; 95531; Subchronic 13 Week Dietary; 821; Rat; Hazleton Laboratories America, Inc., Madison, WI, Project # HLA 6224-150; 7/19/90; Butyrac 200: 4-(2,4-dichlorophenoxy)butyric acid, dimethylamine salt-25.8%; lot# 50215906; Control, 1800 ppm-30/sex/group; 60 and 600 ppm-20/sex/group; Mortalities: Control-1/30 (M),0/30 (F);, 1800 ppm-0/30 (M/F); 60, 600 ppm-0/20 (M/F); 13 weeks-4 week recovery (10 rats/sex/group, control, 1800 ppm); Observations: Histopathology-stomach: erosion of glandular mucosa (1800 ppm) and kidney: tubular cell degeneration (dose related) at 14 weeks-reversible; uterus: fluid in lumen, dilatation of tissue-not reversible. Clinical: RBC, hematocrit, platelet, total protein, albumin, globulin, calcium, serum cholesterol (1800 ppm) significantly reduced Week 14 (M/F). All but globulin, total protein reversed by Week 18. Alkaline phosphatase, alanine aminotransferase (M/F) (1800 ppm) increased Week 14; all but alkaline phosphatase (F) reversed. Body weight gain reduced (dose-related); **Possible adverse effects-persistence of lesions in uterus. NOAEL=600 ppm. NOEL= 60 ppm** (basis-reduced body weight gain (F): 600 ppm)**.** Study previously unacceptable, but upgradeable (test compound formulation, calculation of dosage required) (Moore, 9/28/90) Requested information submitted (50720-022, 95531); Study **acceptable** (Revised Moore, 12/12/90).